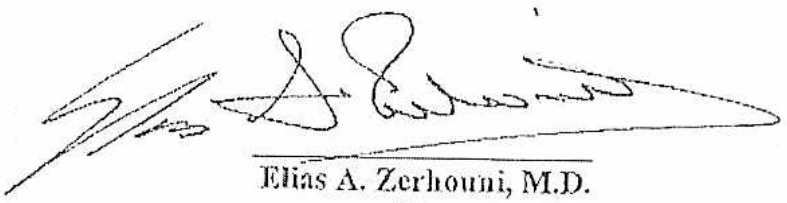
DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

PARKINSON'S DISEASE RESEARCH AGENDA



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Department of Health and Human Services
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Table of Contents

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Executive Summary

In Senate report No. 108-81, the Senate Committee on Appropriations requests the National Institutes of Health (NIH) to report on its implementation of the Parkinson's Disease (PD) Research Agenda, and the Director's plan for Parkinson's disease research.

The NIH has been actively implementing the PD Research Agenda for the past four years. Through grant solicitations, workshops, clinical trials, and numerous other actions, NIH has been addressing every area of research identified in the Agenda. The NIH has also developed appropriate program activities to ensure that emerging areas of research, identified at several PD research meetings, are fully explored. As part of the ongoing implementation process, the NIH Director convened a Summit with leading PD researchers in July 2002, to assess the field of PD research world-wide, and to collect information on the "roadblocks" that may be impeding progress. Following this meeting, NIH scientific and clinical staff developed the participants' recommendations into a Matrix of short-to-long range, and low-to-high risk action items that address these roadblocks. Since the development of this Matrix in December 2002, NIH has made considerable progress on many of these goals. Examples include improved shared resources, better integration and enhancement of clinical studies at PD research centers, and acceleration of therapeutics discovery and translational research. In addition to these program activities, hundreds of researchers supported by traditional investigator-initiated grant programs continue to make groundbreaking scientific discoveries in PD – the ultimate return on the NIH investment.

As NIH enters the final year of the PD Agenda, the implementation of this Agenda and achievement of the Matrix goals continue to be high priorities. At the same time, NIH scientific staff constantly seek out new opportunities for expediting research progress. This combined approach ensures that the Agenda will serve as a foundation for the field of PD research for many years to come, and that the NIH will explore all promising research leads in the field until PD can be both understood and managed effectively.

PARKINSON'S DISEASE RESEARCH AGENDA

Introduction

In its report for the Fiscal Year 2004 budget for the Department of Health and Human Services (DHHS), the Senate Committee on Appropriations stated:

> "*Parkinson's Disease* - ....The Committee is greatly concerned, therefore, to learn that despite strong congressional support for the aims of the Research Agenda, the NIH's projected Parkinson's funding of $242,000,000 for fiscal year 2004 again falls substantially short of the $400,000,000 professional judgment budget estimate cited by the Research Agenda for that year....**The Committee expects the NIH to report to Congress by April 2004, on the steps it is taking to fulfill the Parkinson's Disease Research Agenda and to implement the Director's plan for Parkinson's research**." (Senate report No. 108-81, page 173)

The following report has been prepared by the National Institutes of Health (NIH) of the DHHS in response to this request.

Background

Since March of 2000, the NIH has expended unprecedented effort and has made significant progress on the implementation of the Parkinson's Disease (PD) Research Agenda. The NIH Institutes and Centers (ICs) have initiated extensive programs to develop drug therapies for PD, refine and expand surgical interventions, move gene therapy closer to the clinic, and explore cell transplantation, to name just a few examples. The NIH is also funding more basic science projects than ever before to better understand what triggers PD and how it progresses. Specifically, researchers are examining the brain circuitry that is affected by PD, molecular pathways in affected neurons that lead to their degeneration, and approaches that can prevent or inhibit the progression of PD in animal models. All of these efforts require the scientific contributions of hundreds of dedicated investigators. Although the space limitations of this report do not permit their individual projects to be described in detail, the magnitude of this effort and the critical contributions of these researchers to the implementation process should be recognized.

As part of the Agenda implementation process, NIH engages scientists from the PD research community in periodic reviews of the progress in the field and in the development of recommendations for future action. For example, in January 2002, the NIH held a PD Agenda implementation review consortium meeting at which the participants reviewed the original PD Research Agenda. Although they identified several areas of research for additional focus, it was clear that the research goals highlighted in the Agenda remained critically important and relevant to progress in the field.

The NIH also convened a Summit with outstanding scientists, in July 2002, to gain a better sense of where the field of PD research stands internationally, and to collect information on the "roadblocks" that may be impeding progress. To this end, the meeting was highly productive, and it served as an excellent complement to the January 2002 consortium meeting. The National Institute of Neurological Disorders and Stroke (NINDS) developed the recommendations from the Summit into a Matrix of short-to-long range, and low-to-high risk action items that address these roadblocks. This Matrix does not supplant the Agenda, but rather identifies additional goals that can help facilitate PD research by focusing on potential roadblocks, and places them within a general time frame against which the community can measure progress.

While the Matrix will help to guide further PD planning at NIH, it is designed as a tool for the entire PD community. It includes important responsibilities for voluntary and private funding organizations, and will lead to opportunities for collaboration with other government agencies and the international community as well. The Matrix is intended to be a living document that can be revised and expanded as current goals are achieved and new goals are identified; a copy of the Matrix is provided in the Appendix.

The NINDS leads the implementation of the Agenda and the Matrix, and the newly appointed NINDS Director is strongly committed to continuation of these efforts. However, many other NIH ICs are also actively involved in PD research, reflecting the complex ramifications of the disease. Efforts range from large extramural centers to the encouragement of individual investigators to apply their expertise to the myriad unanswered questions in PD research.

Current Status of Parkinson's Disease Research Agenda Implementation

Science Advances

The NIH is a full four years into the implementation of the PD Research Agenda, and scientific findings are emerging from the research community at an accelerating pace. Investigators supported by many ICs are responsible for these advances, providing a tangible demonstration of the NIH-wide commitment to PD research. The highlights below provide only a small snapshot of the findings reported by NIH-supported scientists in 2003.

Role of Alpha-synuclein in PD

Researchers have known for several years that mutations in the alpha-synuclein gene contribute to the development of PD in some families who have inherited the disorder. Alpha-synuclein protein is also found in Lewy bodies, protein accumulations inside the cell that are a hallmark of both inherited and sporadic forms of PD.

Recently, intramural and extramural researchers collaborating across three Institutes (the National Institute on Aging (NIA), NINDS, and the National Human Genome Research Institute (NHGRI)) found that select families with early-onset PD have a triplication of the alpha-synuclein gene on one chromosome, leading to an approximate doubling of the production of this protein. These data are consistent with the hypothesis that the "dose" of alpha-synuclein present in these individuals' brains is the primary cause of their PD. (Singleton et al., *Science*, 2003, 302:841)

In FY2002, NINDS, the National Institute on Deafness and Other Communication Disorders (NIDCD), the National Institute of Environmental Health Sciences (NIEHS), the National Institute of Mental Health (NIMH), and several private research organizations awarded a group of grants specifically targeted to innovative, high-impact approaches to studying PD. One example of the often unexpected findings from this program involves the use of yeast cells to advance our understanding of PD biology. Specifically, a group of NINDS-supported investigators has now demonstrated that as little as a two-fold increase in the expression of mutant forms of the alpha-synuclein gene causes a catastrophic disturbance in the ability of affected yeast cells to maintain a normal cellular distribution of the alpha-synuclein protein. Not only does the accumulation of

mutant proteins pose a toxicity risk to the cell, but it also compromises the normal function of alpha-synuclein in critical cellular processes. (Outeiro and Lindquist, *Science*, 2003, 302:1772-1775)

Most prior research has suggested that increased expression and aggregation of the alpha-synuclein protein is neurotoxic and contributes to dopamine cell death observed in PD. A recent NIEHS-supported study using an animal model of PD suggests a more complex role for this protein. Exposure of mice to the herbicide paraquat produced death of dopamine neurons in control mice, whereas mice genetically engineered to produce excessive amounts of alpha-synuclein were protected from this toxic insult. These findings suggest that, under some conditions, expression of alpha-synuclein may be beneficial rather than toxic, and that PD may reflect the loss of defensive properties associated with this protein. Understanding the dual role of alpha-synuclein may enable strategies to selectively recruit the beneficial effects associated with this protein as a novel approach to treatment of PD. (Manning-Bog et al., *The Journal of Neuroscience*, 2003, 23(8):3095-9)

Researchers have also recognized that a particular DNA sequence associated with the alpha-synuclein gene varies considerably from person to person, and some reports have suggested that variants of this sequence are associated with sporadic PD. Intramural researchers at NHGRI recently discovered that the sequence length in the variable region was the greatest determinant of the gene's activity level; the composition of the sequence had only a minor effect. This finding will aid researchers in exploring the role of this variable sequence in the development of typical PD. (Chiba-Falek et al., *Human Genetics*, 2003, 113(5):426-431)

Mechanisms of Pesticide-induced Parkinsonism

Several years ago, NIH-supported researchers demonstrated that the administration of the pesticide rotenone to rats could reproduce several key features of human PD, including degeneration of dopamine neurons and motor dysfunction. In a more recent set of studies, this same group has examined the molecular pathways through which rotenone exerts its effects. Their data suggest that rotenone's toxicity is not caused by a depletion of cellular energy, which had been hypothesized previously, but rather from enhancement of oxidative stress in the uniquely vulnerable dopamine-containing neurons. This finding lends additional support for the exploration of antioxidant therapies to treat PD. (Sherer et al., *The Journal of Neuroscience*, 2003, 23(34):10756-10764; supported by

NINDS, NIEHS, and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK))

Treating the Motor Complications of Dopaminergic Therapy

A primary limitation of current dopaminergic treatments for PD is the emergence of response fluctuations and disabling motor side effects after prolonged use. Using both rodent and nonhuman primate models of PD, NINDS and National Institute on Drug Abuse (NIDA)-funded researchers showed that the motor complications could be prevented by a drug that blocks a particular type of nerve cell receptor – those that normally bind a brain chemical called adenosine. These studies provide a strong rationale for the development of adenosine receptor blockers for the treatment of PD in humans. (Bibbiani et al., *Experimental Neurology*, 2003, 184(1):285-94)

Advances in Stem Cell Technology

NINDS-supported researchers have demonstrated that transplantation of dopamine nerve cells derived from somatic cell nuclear transfer (SCNT) can help treat a PD-like condition in mice, the first time SCNT has been used for a brain disorder. In SCNT, the nucleus from an adult cell is transferred to an egg cell, which then forms stem cells that generate cells which can be used therapeutically. The team developed techniques to quickly and efficiently direct mouse stem cells to form several types of specialized brain cells that are potentially relevant to a wide variety of diseases, including dopamine cells for PD, acetylcholine cells for Alzheimer's disease (AD), inhibitory neurons for epilepsy, and glial support cells for multiple sclerosis. (Barberi et al., *Nature Biotechnology*, 2003, 21(10):1200-1207)

Role of Parkin in Neurodegeneration

In 1998, Japanese researchers identified mutations in the parkin gene as being responsible for a rare early-onset form of PD. The NINDS subsequently released a Request for Applications (RFA) on the role of parkin in PD. Two of the grants awarded involved the creation of animals with parkin mutations to enable the study of this gene in normal and disease states. In the first study, parkin mutations in fruit flies implicate mitochondria – the cellular energy generators – in affected systems (Greene et al., *Proceedings of the National Academy of Sciences*, 2003, 100(7): 4078-4083). In a second study, parkin-deficient mice exhibit normal brain structure and numbers of dopamine neurons, but display subtle abnormalities in dopamine system function and behaviors that rely on this system (Goldberg et al.,

The Journal of Biological Chemistry, 2003, 278(44):43629-43635). Together, these data provide important insights into the role that parkin mutations may play in the development of PD in humans.

Involvement of Serotonin in PD

The neurotransmitter dopamine has been the major focus of studies on PD; however, other transmitter systems, such as the serotonin system, are also affected by the disorder. In a recent report, NIA, NIDA, and NINDS-supported investigators used positron emission tomography (PET) – a type of brain imaging – to assess and compare the activity of two brain chemicals: serotonin and dopamine, in individuals with PD and in unaffected controls. The investigators found that binding of both serotonin and dopamine markers was reduced in regions of the brain known to be affected by PD, highlighting the importance of serotonin in the disorder. (Kerenyi et al., *Archives of Neurology*, 2003, 60:1223-1229)

Age-related Sensitivity to Neurotoxicity

Advancing age is the only widely-accepted risk factor for typical PD. However, some investigators have hypothesized that exposure to agrichemicals or other environmental neurotoxicants could further increase the risk that accompanies aging. To test this hypothesis, NIEHS, NIDA, and NINDS-supported researchers compared the effects of agrichemical exposures (paraquat, maneb, or their combination) in mice of different ages. Previous research had already demonstrated that these chemicals induce parkinsonian symptoms in mice. The recent study showed that the "aged" (18-month old) mice were the most severely affected by exposure to the chemicals. These studies demonstrate that the aging dopamine network can exhibit an enhanced sensitivity to neurotoxic pesticides, especially in combination, and that these exposures can lead to permanent neuronal degeneration. (Thiruchelvam et al., *European Journal of Neuroscience*, 2003,18(3):589-600)

New Model for Deep Brain Stimulation Action

Deep brain stimulation (DBS) can effectively reduce several symptoms of advanced PD when applied to the subthalamic nucleus (STN), part of the brain's movement control circuitry. Previously, researchers believed that DBS worked by producing a "reversible lesion" in the STN, and preventing its output to other brain structures. However, recent data from NINDS-supported investigators suggest that DBS may instead work by interfering with the abnormal firing

patterns of the targets of STN neurons, and not by simply silencing the STN itself. (Do and Bean, *Neuron*, 2003, 39:109-120)

Effects of Parkinson's Disease on Memory Structures

The neuroscience community has recognized for many years that the hippocampus is a brain area important for learning and memory. Using magnetic resonance imaging (MRI) of the brain, NIA and National Center for Research Resources (NCRR)-funded investigators compared the volumes of the hippocampus and related structures among individuals with PD, PD and mild cognitive impairment or dementia (PDD), or with AD, to control subjects. The investigators also assessed the participants' mental status and cognitive ability through interviews, neurological examination, and psychological testing. They found that hippocampal volumes were smaller in the three non-control groups, and that a pattern of increasing severity was present, with PD subjects having the smallest reduction in volume, PDD subjects exhibiting a greater reduction, and AD subjects showing the most marked change. These results suggest that this type of MRI imaging might be useful as an early marker for dementia in PD. (Camicioli et al., *Movement Disorders*, 2003, 18:784-790)

Nutrient Intake and PD Risk

Past research has suggested that dietary contributions to oxidative stress may be influential in the development of PD. To examine these associations further, NIEHS supported a population-based case-control study of dietary nutrients and the risk of PD. Through in-person interviews, researchers collected information on food intake frequency, and then normalized nutrient intakes to each person's total energy intake. Results suggested that a high intake of iron, particularly when combined with a high manganese intake, could increase a person's risk of PD. (Powers et al., *Neurology*, 2003, 60(11):1761-1766)

Enhanced Toxicity of Combined Pesticide Exposures

There is mounting epidemiological evidence that exposure to pesticides such as paraquat increases the risk of developing PD. Because several types of agrichemicals are often used in the same area, it is important to evaluate the effect of mixtures on this risk. NIEHS-supported investigators have recently examined the potential for dithiocarbamate (DTC) pesticides to influence the degree of neurotoxicity in a PD mouse model exposed to the herbicide paraquat. The group demonstrated that some commercially available DTCs can increase both the accumulation of dopamine in test-tube preparations of nerve cell connections and

of paraquat in the brains of intact animals. The work suggests that selective DTCs may alter the cellular impact of different chemicals to enhance their neurotoxicity. (Barlow et al., *Journal of Neurochemistry*, 2003, 85:1075-1086)

Head Trauma and PD Risk

Although it is well-established that repeated head trauma can lead to the later development of parkinsonism, the role of a single head injury in typical PD has been controversial. Prior studies that have addressed this question have been limited by their reliance on subject interviews; these studies were often small and could have been biased by subject recall ability. A recent NIEHS-supported population-based case control study used an existing group of subjects with established medical records availability. This access enabled researchers to determine whether any head trauma had been documented prior to the onset of PD. The results of this study demonstrated an increased risk of PD in individuals with a single incident of moderate or severe head trauma, but not in those with a milder incident of head trauma. These data raise intriguing questions about the potential for a single environmental insult to trigger a long lasting cascade of events that culminates in the degeneration of dopamine neurons. (Bower et al., *Neurology*, 2003, 60(10):1610-5)

Involvement of COX-2 in PD

Inflammatory processes involving the enzyme cyclooxygenase-2 (COX-2) have been implicated in neurodegenerative disease, in addition to painful conditions like arthritis. NINDS-supported researchers have recently found that COX-2 expression is increased in dopaminergic neurons – the primary cells that degenerate in PD – in human tissue and in a mouse model of PD. Further, they show that if the toxicant used to produce the parkinsonian symptoms is administered to mice engineered not to express COX-2 (or mice that receive COX-2 inhibitors), these mice do not undergo the same degree of neurodegeneration. These data provide support for further investigations of COX-2 inhibitors as potential treatments for PD. (Teismann et al., *Proceedings of the National Academy of Sciences*, 2003, 100(9):5473-5478)

Relationship of PD to Alzheimer's Disease

As people age, many experience symptoms that could be related to PD and/or AD, but little is known about the relationship between these two disorders. To address this issue, NIA-funded researchers recently investigated the relationship of PD progression to AD risk. The participants, who had no evidence of either AD or

PD at baseline, underwent annual evaluations that included measures of parkinsonian symptoms, as well as in-depth cognitive testing. Over more than four years, parkinsonian symptoms worsened in nearly 80 percent of the participants. The data indicated that people who had more advanced PD-related symptoms also had an increased risk of AD, up to 8-fold higher in people with the most rapid PD progression. These data suggest that advancing PD is associated with cognitive decline and the development of AD. (Wilson et al., *Archives of Neurology*, 2003, 60:539-544)

Drug Intervention for Cognitive Impairment

Some of the most serious non-motor effects of PD are the cognitive deficits experienced by many affected individuals. Recently, NIDA-supported investigators have found that non-human primates treated with the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) display cognitive deficits in addition to the widely-recognized parkinsonian motor impairments caused by this agent. Importantly, this research group has also shown that a nicotine-like drug can improve the primates' performance on certain tasks. At high doses, this drug improves both attention and memory as revealed by a spatial working memory task, and the improvements can last for at least 24 hours. Based on these data, further evaluation of this drug as a therapy for PD-related cognitive impairment may be warranted. (Schneider et al., *Journal of Pharmacology and Experimental Therapeutics*, 2003, 306(1):401-6.)

New Primate Model of PD

For years, the standard non-human primate model of PD has involved the administration of the toxin MPTP. However, this model mimics PD only to a limited degree, since it involves an acute exposure and rapid neuronal loss, and does not lead to some of the critical cellular changes observed in the human disease. To address these issues, NINDS-funded researchers have recently shown that over-expression of normal or mutant human alpha-synuclein via gene therapy can induce progressive parkinsonian neurodegeneration and motor impairment in marmosets. Importantly, the cell death occurs more slowly than with MPTP, providing a time course more comparable to that observed in humans. This model may be advantageous to researchers studying the causes and potential therapies for the disorder. (Kirik et al., *Proceedings of the National Academy of Sciences*, 2003, 100(5): 2884-2889)

Caffeine, Hormones and Parkinson's disease

Although heavy caffeine use is associated with a lower risk of PD in men, researchers have not found the same link in women, and have hypothesized that hormones such as estrogen may explain these differences. A new study from NINDS and NIEHS-supported investigators suggests that either caffeine or hormone replacement therapy alone is associated with lower risk of PD in women. However, women who combine hormone replacement therapy with heavy caffeine use may be one and a half times more likely to develop PD. For this reason, women taking hormone replacement therapy should consider the potential risks of caffeine intake before combining these exposures. (Ascherio et al., *Neurology*, 2003, 60:790-795)

Effects of GDNF on Motor Function

Aged rhesus monkeys can serve as a model of human age-related changes in motor function and also display some behavioral changes that resemble PD, such as decreased home cage activity and slowing on tasks involving upper extremity movements. These changes are thought to be mediated by alterations in release and regulation of dopamine in areas of the brain that support cognition, coordination, and voluntary movement. Researchers supported by NINDS, NIA, and NIMH recently found that administration of glial cell-derived neurotrophic factor (GDNF) to old monkeys improved upper limb motor function to a level comparable to or better than young controls. In regions of the brain that coordinate motor function, release of dopamine by electrical stimulation was significantly increased in aged GDNF recipients compared with control animals. These data demonstrate beneficial effects of GDNF in improving motor function, and could lead to therapeutic approaches to age-related movement disorders such as PD. (Grondin et al., *The Journal of Neuroscience*, 2003, 23:1974-1980)

Parkinson's Disease Genetics

Genetics researchers at the Duke University Udall Center (supported by NINDS and NIA) have conducted recent investigations into the effects of different single nucleotide polymorphisms (SNPs) – small variations in DNA across a population that may be associated with disease susceptibility – in the mitochondria, to determine how these differences might be related to the risk of developing PD. Their results indicated that some specific, less-common SNPs in mitochondrial DNA may be associated with a reduced risk of PD. Interestingly, one of the key "protective" SNPs is found in a gene for a component of Complex I, part of the

mitochondria that is already known to be vulnerable to environmental toxicants. (van de Walt et al., *American Journal of Human Genetics*, 2003, 72:804-811)

Effective Treatments for PD-related Voice Impairments

Past research from NIDCD-funded investigators at the University of Colorado demonstrated that the Lee Silverman Voice Treatment (LSVT) is an efficacious treatment for the voice (and speech) disturbances that can occur with PD. In a recent study, these investigators found that the beneficial effects of LSVT on voice weakening resulting from PD are also accompanied by a normalization of brain activity in regions of the brain associated with speech control. (Liotti et al., *Neurology*, 2003, 60:432-440)

Matrix Implementation Efforts

The July 2002 PD Coordination Summit identified several areas warranting increased focus in the field of PD research. Some areas of special interest, such as translational research, non-motor symptoms of PD, and gene therapy, were also noted at the January 2002 PD Agenda Implementation Review meeting. However, participants at the 2002 Summit also identified new goals for the NIH, and in particular suggested ways in which NIH could help the community overcome research roadblocks. As described above, the NINDS developed these suggestions into a Matrix of very specific goals for the NIH as well as the broader PD community. Although only one full year has passed since the Matrix was established, NIH has made considerable progress on many of the short-term goals. The following section highlights this progress, and a complete list of Matrix goals, along with updates on the implementation of each, can be found at: http://www.ninds.nih.gov/parkinsonsweb/matrix_2003_all.htm

Core Facilities and Resources

Participants in the July 2002 PD Summit enumerated many resource needs of the PD research community, including improved access to molecular tools, gene and brain banks, and transgenic animals. In response, NIH has initiated efforts to expedite access to these and other resources as rapidly as possible.

In September 2002, NINDS awarded a contract to the Coriell Institute for Medical Research to develop the NINDS Human Genetics Repository of data, cell lines, and DNA samples, to enhance the study of the genetic factors contributing to

neurological diseases. PD is one of three diseases that was included in the "ground floor" development of this resource. The Repository continues to archive samples from individuals with PD, and as of December 2003, PD investigators under agreement to make deposits had collected nearly 500 subjects. Of these, approximately two-thirds have PD, and the others will serve as critical controls for genetics studies. As additional investigators develop sharing agreements with the Repository, the accumulation of PD samples will continue to grow. In addition, NINDS announced, in November 2003, that 50 PD and 12 control samples are now available for withdrawal by interested researchers.

In addition to the repository effort, NINDS has added several features to its Parkinson's Disease Research Website (http://www.ninds.nih.gov/parkinsonsweb/index.htm) to enhance the access of PD investigators to needed information on research resources. These include links to information on gene vectors, antibodies, and animal models that will be useful to a wide range of PD investigators.

The NCRR strongly supports the development of animal models of human disease, and contributes to the availability of mutant mouse models for the study of PD and Parkinson's-related diseases through its animal resource programs. Specifically, the Induced Mouse Resources Program maintains mutant mouse strains with applications to PD research, including genetically-modified mice that express the human form of a mutant alpha-synuclein gene. These mice exhibit behavioral impairments, intracellular accumulation of alpha-synuclein throughout the nervous system, and nerve fiber degeneration. In addition, a mouse model of PD produced by "knocking out" a type of dopamine receptor is also available.

In addition to mouse models of PD, NCRR also supports the study of non-human primate models of the disease, through its National Primate Research Centers. For example, investigators at the University of Wisconsin National Primate Research Center are studying the transplantation of neural progenitor cells, differentiated from rhesus monkey embryonic stem cells, into primates treated with MPTP. They are attempting to stimulate the neuroprogenitor cells to differentiate into dopamine neurons. These studies are still very preliminary but are designed to revive/replenish the neurons that are affected by the MPTP treatment. In addition, investigators at the New England National Primate Research Center have developed a new radioactive tracing compound, Altropane, which has a high affinity and selectivity for dopamine transporter sites in the

striatum, and may be useful in the future as a diagnostic tool for detecting domaminergic activity in individuals with probable PD.

Lastly, the National Center for Complementary and Alternative Medicine (NCCAM) supports a core center on Complementary and Alternative Medicine in Neurodegenerative Diseases at Emory University with a strong emphasis on PD. This center supports both clinical and basic research on PD, including pilot projects on the effects of neuromuscular massage therapy on PD symptoms, the effect of wellness interventions on quality of life, and a study of the use of creatine monhydrate supplementation for PD patients. In addition to the pilot projects, the core center supports independent research projects on Chinese exercise regimes for PD patients, investigations of the efficacy of valerian (a dietary supplement) for sleep disturbances in PD patients, and a study of the effect of transcranial magnetic stimulation for symptom relief in PD.

Parkinson's Disease Research Centers

Recommendations made at the PD Summit also highlighted several issues related to research at Udall and other PD research centers across the country: better integration of basic, translational, and clinical research; shared research facilities, tissue and data banks; and improved coordination and standardization of data collection. Ultimately, centers should strive to work as a patient-centric system in which community physicians, research centers, and NIH are all part of a cohesive network.

To develop a more detailed plan to address these issues, NINDS sponsored a meeting of outside researchers and NIH staff in March 2003. Specific topics of discussion included the streamlining of clinical data collection, and the development of minimum clinical and pathological data sets that would be collected along with human PD tissue samples. To begin to address these issues, NINDS announced in July 2003 that it would offer competitive supplements to Udall researchers to enhance their clinical research programs. The NINDS has also worked with the extramural research community to develop the minimum data sets described above, and has made them publicly available via links on its PD Research Website (http://www.ninds.nih.gov/parkinsonsweb/clinical_research.htm). In addition, NINDS, along with the NIEHS, released an RFA in November 2003, to solicit applications for a Parkinson's Disease Data Organizing Center that will collect clinical data across Udall centers, NIEHS PD research centers, NIA-supported AD

centers, and others, to make data collection more consistent, and ensure that these data are widely available. NIEHS involvement will help to facilitate the inclusion of data on environmental exposures and PD.

Public-Private Partnerships

Summit participants also recommended that the Director of NIH appoint an individual to serve as a liaison to the PD scientific and voluntary communities, and to other Federal funders of PD research. They expressed the hope that this individual would provide both leadership and scientific guidance to quickly exploit research advances and facilitate cooperation among all parties with a vested interest in PD research.

In response, the NIH Director asked an experienced member of the NINDS program staff to serve as a liaison to these groups, and as a result, NIH staff have held conference calls with their representatives on several occasions throughout the year. Topics of these meetings have ranged from recruitment for clinical trials to the organization of an international meeting on PD, and have resulted in good progress on both efforts. For example, the international meeting is being planned for 2005, and is expected to involve government and non-government funders of PD research, along with several leading scientists. It is hoped that this meeting will serve as a first of its kind in the PD community to: 1) bring together the basic science and clinical research communities to discuss research findings; 2) provide a forum for members of the voluntary PD community to learn about recent scientific findings and discuss quality of life and other issues of interest; and 3) encourage a productive dialogue among these different groups.

Basic Cell Biology Research

Summit recommendations in the area of basic cellular studies in PD included improving our understanding of the alpha-synuclein and parkin proteins, elucidating the role of the ubiquitin cellular waste disposal system in PD, and identifying cellular mechanisms (e.g., mishandling of proteins) that may be common to PD and other neurodegenerative diseases, like Alzheimer's and Huntington’s diseases.

To continue a dialogue with the research community on these issues, NINDS and NIA sponsored a workshop in June 2003, entitled "Cell Biology of Parkinson's Disease and Related Neurodegenerative Disorders." Topics of the presentations included protein accumulation and breakdown mechanisms in neurodegeneration,

new genetic findings in PD, and proteins (such as mutant forms of amyloid, tau, and alpha-synuclein) that are common to multiple neurodegenerative diseases. In addition, several investigators funded under two March 2000 grant solicitations on parkin and synaptic proteins presented the results of their NINDS-supported research.

Gene Discovery

To expedite our understanding of the contributions of genetics to PD, Summit participants recommended enhancing the search for new families with PD in order to identify more genes and their protein products implicated in the disease, and to carry out detailed chromosomal mapping studies once genes are identified.

As described above, NINDS awarded a contract for a DNA repository to house PD samples in September 2002. Over the past year, NINDS staff have been working closely with the contractors to enhance contributions from PD clinical researchers. These efforts are naturally targeted towards expansion, with DNA samples from new families welcomed. To further facilitate these efforts, NINDS announced an administrative supplement program, in May 2003, to assist researchers who have an ongoing NINDS clinical project to perform additional blood sample collection. The supplement will defray some of the added costs of collecting and characterizing samples for submission to the NINDS Human Genetics Repository.

In March 2003, NINDS, NIA, NIDA, and NIEHS issued a joint Program Announcement with Set-aside (PAS) in order to solicit applications on the identification of susceptibility genes that contribute to genetically complex disorders affecting the nervous system, or to the clinical manifestations of these conditions. Although no grants on PD genetics have been awarded thus far, it will continue to be a disease of interest under this PAS.

Translational Research/Therapeutics Development

In addition to the research areas described above, the Summit recommendations also included the translation of novel therapies (including but not limited to cellular and gene therapies) from preclinical studies to clinical trials as an important ongoing priority of the field.

Following the PD Summit, NINDS, with some support from the NIH Director's Discretionary Fund, awarded a grant in September 2002 for a large, multi-center,

multidisciplinary, preclinical investigation of both dopaminergic enzyme gene therapy and neurotrophic gene therapy in non-human primate models of PD. This Parkinson's Disease Gene Therapy Study Group has accomplished its first-year milestones, including the creation of a stable colony of parkinsonian primates, and the molecular development of regulatable viral vectors to be used in the study.

In addition, NINDS launched the Neuroprotection Exploratory Trials in PD (NET-PD) in April 2003; NET-PD is a major series of cooperative clinical studies designed to evaluate drug therapies that have the potential to slow the progression of PD. Extensive planning, infrastructure development, and rigorous review of candidate therapies preceded the launch of the first two phase II trials. Over the past nine months, 42 sites have been recruiting individuals with early, untreated PD to participate in trials of minocycline (an antibiotic related to tetracycline) or creatine (a common nutritional supplement and possible antioxidant). Recruitment for both studies progressed rapidly, and was completed as of November 2003. The NINDS anticipates that enrollment for the next two studies, designed to test coenzyme Q10 (a health supplement and antioxidant) and GPI-1485 (a proprietary compound with growth factor properties), will begin in early 2004. The NET-PD research group will proceed with phase III trials of the drugs that show promise in these phase II studies.

Nonmotor Symptoms of Parkinson's Disease

Summit participants also emphasized the need for clinical studies of non-motor symptoms in PD to be an ongoing research priority.

NIH ICs are already engaged in providing support for some clinical studies of non-motor symptoms. For example, NINDS intramural researchers are studying the safety and effectiveness of donepezil (Aricept) for treating mild dementia in patients with PD. In addition, the NCCAM supports a clinical trial to determine if S-Adenosylmethionine (SAM-e; sold as a dietary supplement) is a safe and effective therapy for depression in PD. Previous studies indicate that 30 to 50 percent of patients with PD suffer from depression. However, commonly prescribed antidepressants are often not appropriate for individuals with PD, since some can exacerbate already compromised motor functions. This study will also investigate the underlying mechanism of SAM-e as it relates to depression and the motor function symptoms of PD.

In addition to this research, NINDS and the National Heart, Lung, and Blood Institute (NHLBI) issued a PAS in June 2003, to encourage studies on sleep disturbances, a debilitating problem in PD and Parkinson's-related neurological conditions. Studies of the natural history of symptoms, mechanistic studies of the sleep disturbances in PD, and studies of the sleep-related effects of pharmacotherapies for PD, would all be relevant to this solicitation.

The NINDS also recognizes that clinical depression contributes to a reduced quality of life and increased disability for many individuals with PD. As a first step in improving the diagnosis of depression across PD patients, NINDS sponsored a workshop in December 2003 to initiate a discussion with the extramural research community on the merits of existing depression rating tools. Participants identified several areas of concern with some of the most commonly-used tools, and will work with NINDS staff to develop provisional diagnostic criteria and an evaluation of existing rating scales, with possible recommendations for action within the clinical community. Improvements in the ability to diagnose individuals who have depression along with PD will be essential to the development of future clinical trials of therapeutic interventions.

Gene/Environment Interactions

A recent NIEHS program announcement, "Gene-Environment Interactions in Neurodegenerative Disease" will focus on promoting research on identified gaps in neurodegenerative disease. The first year of this initiative is emphasizing support for research in gene-environment interactions in amyotrophic lateral sclerosis (ALS). Next year's focus will be influenced by the results of a June 2004 planning meeting on "Environmental Influences in Neurodegenerative Disease: Synthesis and Next Steps," which is described in more detail in the "Environmental Contributions to PD" section of this report.

Biomarker Development

Participants at past PD meetings and workshops had identified biomarkers – biological markers of the presence or progression of a disease – as a critical need in the PD research community. Attendees at the 2002 Summit reiterated this recommendation.

As a first step to explore the use of imaging tools as biomarkers for the assessment of PD, NINDS sponsored a workshop in July 2003 to consider the use of imaging biomarkers as either additional measures or as endpoints in clinical

trials, the capability of current imaging technology, including molecular "tags," and the feasibility of using imaging measures consistently in multicenter clinical trials. Participants are developing a paper with NINDS staff, to recommend: 1) methodological changes in studies to determine how imaging measures relate to clinical endpoints, and 2) development of new markers to better capture the degenerative process and more of the clinical features of PD.

General Implementation of the PD Agenda

Although many of the program activities initiated by NIH staff in the past year have been directly related to the PD Matrix, the implementation of the PD Agenda is also moving forward in many critical research areas. Examples of these efforts include the following programs:

Stem Cell Programs

Over the past two years, NIH has enhanced its support for stem cell research through a number of grant solicitations, workshops, and other initiatives. As an example of these efforts, NINDS was joined by NIDA, NIDCD, the National Institute of Alcohol Abuse and Alcoholism (NIAAA), and the NIA in releasing a PAS on "Interactions Between Stem Cells and the Microenvironment in vivo" in September 2003. This announcement invites applications that study the unique signaling between stem and precursor cells and the local environment within different parts of the host organism's nervous system. The objective of this initiative is to promote a thorough exploration and characterization of the two-way communication between stem and stem-like cells and the three-dimensional environment that they encounter in vivo, under normal and compromised states, such as with aging or following injury, disease or drug exposure. This announcement would be applicable to a broad range of neurological disorders, including PD.

The NIA also issued an RFA in October 2003, entitled "Biology of Stem Cells in Aging." This solicitation was designed to encourage studies of stem cells and the tissue environment as a function of aging, stem cell integration into aging tissues, and the role of stem cells in degenerative disorders of aging – including PD.

The NIH is also committed to ensuring that investigators are sufficiently prepared to manage stem cells as they become available, and is providing support for five

short-term training courses in human embryonic stem cell culture techniques. These training courses, held in 2003 (and future years) at various locations, include hands-on experience to improve the knowledge and skills of biomedical researchers to maintain, characterize, and utilize human embryonic stem cells in basic research studies. The courses are available to investigators in research areas of interest and to all institutes and centers of the NIH.

In addition to its support of training, the NIH has made many efforts to make human embryonic stem cells (hESCs) available to investigators. The NIH has issued a number of infrastructure awards to fund the hESC providers to "ramp up" and to make available numerous approved lines of hESCs for investigators who wish to work on them. As a result, up to seventeen approved lines are now available to investigators. This has enabled a number of researchers to begin developing "best practices" to derive a type of dopaminergic neuron from hESCs that could replace lost cells in PD. The NINDS has also issued several rounds of administrative supplements (beginning in FY2002 and through FY2003) to enable its grantees to begin working on human stem cells. Some researchers who received these supplements are studying dopaminergic neurons.

In addition to these extramural research activities, the NIH Intramural Research Program established an NIH Stem Cell Unit in April 2003, to develop side-by-side comparisons of the available cell lines on the NIH hESC Registry, in order to help researchers identify the stem cell lines that are most suitable for their intended experiments. Specifically, the Unit will identify – and share with the research community – the similarities and differences between the available hESC lines when subjected to a standardized paradigm. These data will give the scientific community information about the properties of available lines, so scientists can make an informed choice when ordering one or more of these lines. Although the assays performed by this Unit will be overseen by a steering committee of leading stem cell biologists in both the extramural and NIH intramural research communities, a scientist in the NINDS intramural research program will provide day-to-day direction for this unit.

Drug Screening

For the past several years, NINDS has made funds available through several different mechanisms to enhance the access of academic investigators to high-throughput drug screening resources. These efforts have been focused to date on neurodegenerative diseases, including PD. An initial supplement program

funded investigators – the Neurodegeneration Drug Screening Consortium – to perform rapid "in vitro" (i.e., in a test tube or dish) screens of Food and Drug Administration (FDA)-approved and other bioactive compounds, in order to identify candidates for further exploration. The open sharing of data among the researchers in this Consortium is an important component of the project, and has allowed a great deal of cross-collaboration across laboratories and an enhanced capacity to screen drugs in several models of neurodegenerative disease. Several drugs appear to show promise from the Consortium screens, and at least eight of these are now being explored in more advanced models of disease, as described below.

To further accelerate this research, NINDS announced, in March 2003, that it would offer additional competitive supplements to investigators interested in testing candidate drug therapies in rodent models of neurodegenerative diseases. NINDS is funding three PD-related supplements, and The Michael J. Fox Foundation for Parkinson's Research provided support to expand this effort, so that additional awards with particular relevance to PD could be made. As a result of this program, two of the compounds identified as promising candidates in the initial Consortium screen are now being evaluated in animal models of PD. In addition, neuroprotective compounds identified in other NINDS-funded projects are also being tested. In total, approximately 17 drugs are being tested in animal models of PD as a result of these supplements. Since all of the compounds tested in this program were selected for neuroprotective activity, others of the approximately 40 drugs being tested in neurodegenerative mouse models may also be relevant for further testing in PD. As with the Consortium screening effort, this new supplement program will facilitate data sharing and comparisons among the funded groups so that promising candidates can be moved quickly to other relevant disease areas. As this project moves forward and as new drugs enter the testing pipeline, any candidates that show promise in animal models of PD will be considered for evaluation in the NINDS NET-PD clinical trials.

As an additional step to help investigators move promising therapeutics into clinical testing, NINDS also announced, in October 2003, that it will provide supplements to investigators for small, focused projects that will accelerate preclinical therapeutics development. Under this announcement, the highest funding priority will be given to studies that are specifically designed to support an Investigational New Drug (IND) application for clinical testing, and that form part of a well-developed plan for pursuing an IND.

Lastly, NIH is engaged in broad-scale efforts, including Roadmap initiatives, to improve drug development across many neurological and non-neurological diseases, including the creation of libraries of compounds to test, drug screening facilities, and databases that will facilitate researchers' access to information. The NIH has developed these resources specifically to accelerate the evaluation of potential therapies and the translation of the most promising candidates to clinical trials.

Environmental Contributions to PD

The NIEHS Collaborative Centers for Parkinson's Disease Environmental Research (CCPDER) Program was launched in September 2002 with the establishment of a national network of three Centers devoted to studying environmental factor causation in PD. These Centers are also evaluating the influence of environmental factors at a mechanistic level, in order to develop rational prevention and intervention strategies for the disease. For example, one focus across the Centers will be the interaction of pesticides with cellular mechanisms involved in protein degradation, oxidative stress, membrane transport and regulation of endogenous dopamine levels.

Two important features of the CCPDER program are collaboration across scientific disciplines and involvement of the lay PD community. The first goal will be achieved as the Centers bring together geneticists, clinicians, epidemiologists and basic laboratory scientists studying PD. Annual meetings of CCPDER investigators are already taking place, and future meetings will involve NINDS staff as well to facilitate information exchange and linkages between the CCPDER and NINDS-supported Udall Centers (which co-exist at two research institutions). The second goal will be achieved in several ways, including participation of advocates as members of External Advisory Boards of each CCPDER Center and through planned collaborative design and evaluation of a CCPDER website that facilitates information exchange with the PD scientific and lay communities.

During their first year of operation, the Centers have worked in close cooperation with NIEHS program staff to successfully establish the overall governance structure of the network. A Steering Committee was formed and has guided the solicitation and evaluation of applications for small research development grants awarded by each Center. An inaugural scientific workshop on an emerging scientific topic in PD, proteosomal function/dysfunction, was held in July 2003.

In addition to these joint activities, the individual Center components have made significant progress on the research projects proposed in their applications, and NIEHS support has facilitated interdisciplinary collaborations within each of the Centers that would not have been possible otherwise.

The NIEHS also supported the Twenty-first International Neurotoxicology Conference, held in Honolulu, Hawaii, in February 2004. A special session entitled "Parkinson's disease, Environment and Genes" highlighted current research in environmental risk factors and the creation of new research paradigms to address gene-environment interactions in disease initiation and progression.

In June 2004, the NIEHS will sponsor a meeting on "Environmental Influences in Neurodegenerative Disease: Synthesis and Next Steps," to bring together current NIEHS grantees studying neurodegenerative diseases such as PD and AD, as well as other non-grantee experts. The goal of this meeting will be to highlight recent progress in elucidating environmental etiologies of neurodegeneration; to promote cross-fertilization of ideas among researchers, diseases and disciplines; and to identify and prioritize data gaps, future resource needs, and research opportunities. The results of this meeting will help gauge the effectiveness of recent NIEHS targeted program activities and will provide a template for crafting a five-year research agenda for understanding environmental contributions to neurodegenerative disorders. The NINDS, NIA and NIMH will be invited to participate in this meeting to facilitate joint program planning for future initiatives.

Lastly, in response to a PA on “The Fetal Basis of Adult Disease,” the NIEHS awarded four grants in FY2003 that were focused on PD. These studies will utilize animal models to examine gestational exposure to pesticides and infectious agents as potential risk factors for PD.

Consortium on Deep Brain Stimulation for PD

The NIH DBS Consortium is a core group of researchers funded under a series of NINDS/NIA/NIMH-sponsored RFAs to explore DBS and its therapeutic applications from different disciplinary perspectives. Plans for the Consortium specified that an annual workshop/meeting of grantees should be organized to develop collaborations among members of the Consortium and promote an enhanced sense of community among DBS researchers and practitioners.

The second of these meetings took place in Washington, DC, in September 2003, and included interested members of the DBS community, in addition to the core group of awardees. As a result, an international group of physicians, basic scientists, patient advocates, industry representatives, and governmental officials participated in the identification of opportunities for collaboration within the DBS research community. The long term objective of the group is to develop better and more broadly applicable therapies through an improved understanding of the mechanism of action of DBS, as validated by rigorous clinical trials.

Collaborative Research on Aging

In December 2002, NINDS joined the NIA on the release of a grant solicitation entitled "Collaborative Studies on Alzheimer's Disease and Other Neurodegenerative Diseases Associated with Aging." The purpose of this RFA was to facilitate collaborative cross-disciplinary and multi-institutional approaches that will contribute new and vital information about the clinical and pathological course of normal aging and the neurodegenerative diseases associated with aging. As a result of this solicitation, NINDS has funded a collaborative group of Alzheimer's Disease Research Center investigators to study the differences between AD and "dementia with Lewy bodies," a degenerative disorder that is related to PD, at the clinical, pathological, and molecular levels.

Voice and Speech Disturbances in PD

The NIDCD and the NIH Office of Rare Diseases co-sponsored a workshop on "Neurologic Motor Speech Disorders in Adults," held in June 2003. A number of speech scientists and neuroscientists discussed issues in neuro-imaging of speech production disorders, neural control of the motor speech system and how speech is being assessed in neurologic disease. The workshop was well-attended by many NIDCD-supported investigators. Although PD was not the focus of this workshop, much of the discussion was relevant to PD and is expected to influence future research applications in this area.

Conclusions

As NIH enters the final year of the PD Agenda, implementation of this Agenda and achievement of the Matrix goals continue to be high priorities. At the same time, NIH scientific staff constantly seek out new opportunities for expediting research progress. Together with the growing NIH portfolio of investigator-

initiated research on PD, this combined approach ensures that the Agenda will serve as a foundation for the field for many years to come, and that the NIH will explore all promising research leads until PD can be both understood and managed effectively.

Appendix

Parkinson's Disease Matrix: Research Community Goals

Overview

Since March of 2000, the National Institutes of Health (NIH) has expended tremendous effort and has made significant progress on the implementation of the Parkinson's Disease (PD) Research Agenda. As part of the implementation process, NIH convened a summit with several outstanding scientists in late July 2002 - to gain a better sense of where the field of PD research stands internationally, and to collect information on the "roadblocks" that may still be impacting progress. To this end, the meeting was very successful, and it served as an excellent complement to the PD Agenda implementation review consortium meeting that was held by NIH in January 2002.

As the next step in the NIH PD planning effort, the National Institute of Neurological Disorders and Stroke has developed the following recommendations from the July meeting into a matrix of short-to-long range, and low-to-high risk action items in order to address some of these roadblocks. While this matrix will help to guide further PD planning at NIH, it is designed primarily as a tool for the entire PD community. It includes important responsibilities for voluntary and private funding organizations, and will hopefully lead to opportunities for collaboration with other government agencies and the international community as well. This matrix is intended to be a living document that can be revised and expanded as current goals are achieved and new goals are identified.

Participants at the January 2002 consortium meeting reviewed the original Agenda, and although they identified several areas of research for additional focus, it was clear that the research goals highlighted in the Agenda are still critically important and relevant to progress in the field. Thus this matrix does not supplant the Agenda, but rather identifies additional goals that can help facilitate PD research by focusing on potential roadblocks and places them within a general timeframe against which the community can measure progress.

Core Facilities and Resources - Expanded and accelerated implementation

General comments on core facilities/resources from participants at the July meeting: Greater access to resources such as molecular tools, gene banks,

transgenic animals, cell lines, gene vectors, brain banks, and primate facilities, etc. continues to be an urgent need of the PD field. The primary goal of improved access is to help scientists achieve research goals such as the discovery of remaining PD genes/proteins, susceptibility genes/proteins, dopaminergic and non-dopaminergic cellular "actors" in the pathogenesis of PD, as well as the translation of preclinical studies of cell replacement, gene therapy and other therapeutic approaches. Increased, broad access to core resources and the development of new resources will result in greater synergy and productivity among researchers, reduce the costs of research, and facilitate the entry of new investigators into the PD field.

General Resources
Goal A: By the end of FY2003, expand website-based resource sharing to include additional resources recommended at both the 2002 PD Summit meeting and the 2002 Udall meeting (see above list). (Low Risk/Short Term) Primary lead: NINDS

Gene Therapy Resources
Goal B: By the end of FY2003, develop links on the NINDS PD Web to enable investigators to access application forms for obtaining vectors from the National Gene Vector Laboratories, and to obtain information from the Food and Drug Administration that can instruct investigators in the use of these vectors for translational research. (Low Risk/Short Term) Primary leads: NINDS, NCRR

Animal Models
Goal C: By the end of FY2004, form steering committee and develop guidelines to facilitate greater sharing of mouse models of PD among NIH-funded investigators, and continue to promote the deposition of the most successful models into genetically-engineered mouse resources (e.g., the Jackson Laboratory, and the Mutant Mouse Research Resource Centers) (Low Risk/Short Term) Primary leads: NINDS, NCRR

Brain Banks
Comments from participants at the July meeting: As part of the PD research community's continuing effort to coordinate brain banks, research centers, etc., a set of core assessments for individuals with PD should be established and validated. This would include standardized diagnostic criteria using neuro/neuropsych/psych assessments, autopsy/pathology/access procedures that

can be used across research centers, improved diagnostic tools (e.g., biomarkers), and better links with clinical centers. In addition, the PD community should to be encouraged to educate patients and their families on the research benefits of donation.

Goal D: By the end of FY2003, develop partnerships with PD voluntary organizations to initiate outreach efforts to the PD patient community regarding the need for increased participation in making donations to brain banks. (Low risk/Short term) Primary lead: The Parkinson Foundation

Goal E: By the end of FY2003, convene a meeting of the extramural research community and NIH staff to develop consensus on standardized assessment tools for PD, including clinical and imaging diagnostic definitions of PD for brain banking, brain banking protocols, etc. following the groundwork established by Lees, Gilman, and others. (Medium risk/Short term) Primary lead: NINDS

Goal F: By the end of FY2006, establish a minimum of five coordinated brain banks internationally to serve the entire PD community. Standardized assessments developed at the 2003 meeting would be incorporated into methodology used by all banks. (Low risk/Medium term) Primary leads: NINDS, NIA

Integration of PD Research Centers

Comments from participants at the July meeting: A network of integrated centers could link basic, translational, and clinical research, and could further the development of outcome tools, brain banks, and biomarkers. These centers could potentially include cores (e.g., for clinical pathology), tissue and data banks, and formal coordinating mechanisms (including a data coordinating center, development of standards for data collection, joint center meetings, mechanisms for community outreach, acceleration of clinical trials, add-on studies for clinical trials, and links with industry). Importantly, the ultimate goal of improving the integration of centers is to create a patient-centric system in which community physicians, research centers, and NIH are all part of a cohesive network. With such a system, information on patients can be better captured and managed, and research can be integrated at both the basic and clinical levels.

Goal A: By the end of FY2003, hold a data-gathering meeting/workshop including Udall Center investigators, Collaborative Centers for Parkinson's Disease Environmental Research (CCPDER) investigators, representatives from the Alzheimer's Disease Research Centers (ADRCs), NIH staff, and the voluntary community, to identify needs for better organization and integration of PD research centers. Topics of focus at the meeting could include center priorities (basic/translational/clinical), brain banking, cores, data coordination, and the development of biomarkers. An additional topic of discussion would be methods of better integrating the patient component into studies, maximizing the usefulness of clinical databases, and involving community clinicians in research efforts and clinical trials. Follow-up would include consideration of a coordinating PD center as a possible mid/long-range goal. (Low Risk/Short Term) Primary leads: NINDS, NIEHS, NIA

Goal B: Include ADRC and CCPDER investigators in annual meeting of NIH Udall Center investigators. (Low Risk/Short Term) Primary lead: NINDS

Goal C: By the end of FY2003, release a Notice in the NIH Guide (or utilize another competitive solicitation mechanism) as a means to address some of the immediate needs identified at the 2003 data-gathering meeting (described above). Coordinate this effort with all interested agencies, including PD Voluntary organizations. (Low Risk/Short Term) Primary lead: NINDS

Goal D: By the end of FY2003, develop NIH and PD community consensus on the data set (i.e., the clinical information agreed upon as that best collected to accompany DNA samples, brain tissue, or for other clinical studies) for PD that will be used by the Udall Centers, CCPDERs, and ADRCs. (Medium risk/Short term) Primary leads: NINDS, NIEHS, NIA

Public-Private Partnerships

Improved Coordination

Comments from participants at the July meeting: In addition to improved core resources and improved centers structure, another short-term organizational goal includes formal management at the level of the NIH director to ensure coordination between NIH agencies and outside agencies worldwide (including patient groups and industry), and the international research community. A "PD

Champion," located at NIH, could be responsible for coordinating Parkinson-related activities across the NIH Institutes and Centers, and between the NIH, extramural investigators, the private foundations, and international contacts - with direct reporting and accountability to the NIH director. He/she could also help to continually assess the international portfolio of PD research, and define gaps in knowledge and infrastructure that could impede progress. Lastly, this individual would provide leadership and research support to quickly exploit research advances, as well as interact intensively with both intramural and extramural researchers and patient advocates.

Goal A: By the end of FY2003, establish a formal mechanism for continuing dialogue between NIH, PD voluntary groups, other federal agencies, industry, etc. to identify opportunities for public-private partnership (e.g., facilitation of the outside groups' efforts to educate and raise awareness regarding recruitment for PD clinical trials). Achievement of this goal would require continued regular meetings of the NIH PD Coordinating Committee and the PD Implementation Committee. (Low Risk/Short Term) Primary leads: NINDS (federal coordination), The Parkinson Foundation and the American Parkinson Disease Association (coordination of the voluntary community)

Goal B: By the end of FY2003, the NIH director will identify a member of the NIH staff who will help to coordinate PD activities across Institutes and Centers and will help to facilitate communications between NIH, outside agencies and investigators, and the PD voluntary organizations. This staff person will report directly to the NIH Director in addition to his/her own Institute/Center Director. (Medium risk/Short term) Primary lead: NINDS

International Meeting

Comments from participants at the July meeting: An annual meeting of the PD international community is needed; in particular one that would include representatives of industry, academia, NIH, private foundations, and members of the international PD research community.

Goal C: By the end of FY2004, private voluntary PD organizations will evaluate the current international meetings on PD and sponsor a large global meeting that addresses current perceived deficiencies. (Medium risk/Short term) Primary lead: The Parkinson Foundation

Basic Cell Biology Research - Understanding cell death, alpha-synuclein, parkin, ubiquitin pathways

Comments from participants at the July meeting: It will be important to address a number of basic questions in the cell biology of PD that remain unanswered. These include achieving a better understanding of the normal function of alpha-synuclein and parkin, elucidating the role of the ubiquitin system and its regulators in PD, and identifying cellular mechanisms (e.g., mishandling of proteins) that may be common to PD and other neurodegenerative diseases, like Alzheimer's disease and triplet repeat disorders.

Goal A: By the end of FY2003, convene a meeting of investigators funded under the FY2001 joint "fast-track" R21 program to share data and assess progress on the topics listed above and others. (Low Risk/Short Term) Primary lead: NINDS

Goal B: By the end of FY2003, convene a separate meeting of investigators funded under the FY2000 NINDS parkin and synuclein RFAs, as well as other investigators in the field, to share data and assess progress. (Low Risk/Short Term) Primary lead: NINDS

Goal C: By the end of FY2003, give a presentation at the NIH symposium during the annual meeting of the American Society for Cell Biology focusing on the emerging applications of basic cell biology (e.g., protein clearance, etc.) to PD and other degenerative disorders of the nervous system. (Low Risk/Short Term) Primary lead: NINDS

Gene Discovery

Comments from participants at the July meeting: It is important to continue to search for new families with PD in order to identify more genes and their protein products implicated in the disease, to perform linkage analyses in families with cases of PD that have not been linked to currently known chromosomal loci, and to carry out fine-mapping and rapid gene identification studies in all PD families (the development of appropriate guidelines for genetic testing must be a priority in this process). Specific goals could include the molecular cloning of disease genes for known loci (e.g., PARK 3 to 9) and the identification of additional genes with a role in PD. The development of transgenic animal models based on these discoveries will help to elucidate pathogenic mechanisms.

Goal A: By the end of FY2003, issue a Program Announcement with Set-aside funds (PAS) on Gene Discovery for Complex Neurological and Neurobehavioral Disorders, including PD. This PAS will include standards for collection and sharing of samples that are consistent with those established in other PD goals. (Medium risk/Short term) Primary lead: NINDS

Goal B: By the end of FY2005, identify multiple families with PD and collect a minimum of 50 samples for the NINDS Human Cell Line and DNA Repository. (Medium risk/Short Short term) Primary lead: NINDS

Translational Research/Therapeutics Development

Comments from participants at the July meeting: The translation of novel therapies (including but not limited to cellular and gene therapies) from preclinical studies to clinical trials continues to be an important priority of the PD field.

Goal A: By the end of FY2004, complete the first set of milestones for the NIH-funded Parkinson's gene therapy translational project, including stable gene delivery to the brains of parkinsonian animal models and construction of regulatable vectors. (Medium risk/Short term) Primary lead: The Parkinson's Disease Gene Therapy Study Group (PDGTSG)

Goal B: By the end of FY2010, evaluate the effectiveness of four or more interventions to slow the progression of PD or other neurodegenerative diseases in patients. (High risk/Long term) Primary lead: NINDS

General Roadblocks to Advancing PD Research

Intellectual Property (IP) issues

Comments from participants at the July meeting: As the field has moved to implement the PD Agenda, numerous patent/intellectual property issues have arisen that threaten to hamper research in PD and many other areas of neuroscience. Translational research is particularly vulnerable to these roadblocks. Convening a summit to discuss IP roadblocks would facilitate discussion between the involved parties (e.g., pharmaceutical company representatives, academicians, federal agency representatives, and their

international counterparts). Other approaches include the development of a "national IP clearinghouse," and/or a more systematic approach to licensing. Other fields have successfully managed these IP issues (e.g., cancer) and the neuroscience research community could benefit from these precedents.

Goal A: Address the IP/tech transfer concerns summarized above. (High risk/Medium term) Primary lead: NIH Office of Technology Transfer

Stem Cell Distribution

Comments from participants at the July meeting: A priority in the field of stem cell research that would facilitate progress in PD is the establishment of an NIH-funded stem cell bank. Access to such a resource could facilitate more extensive evaluations of the potential for stem cells in replacement therapies as well as localized delivery of therapeutic compounds to the nervous system.

Goal B: Address the concerns related to stem cell distribution summarized above. (High risk/Medium term) Primary lead: NIH Stem Cell Task Force

Training

Comments from participants at the July meeting: The field of PD research would benefit from increasing the number of talented researchers in the field, in particular new investigators and individuals who are experienced in designing and managing clinical trials.

Goal C: Evaluate options for the recruitment of new investigators to the field of PD research, and for the training of investigators who are managing clinical trials and/or conducting observational studies in PD; conduct further investigation into existence of unique roadblocks for investigators in the PD field that are not currently addressed by federal and non-federal training opportunities. (Low risk/Short term) Primary lead: NINDS

Clinical Trials of Non-motor Symptoms

Goal: Use mechanisms available through clinical trial programs and intramural research programs at the individual NIH ICs to facilitate clinical trials of non-motor symptoms in PD.
(Low risk/Medium term) Primary leads: NINDS, NIMH

Understanding Gene/environment Interactions

Comments from participants at the July meeting: In addition to enhancing our understanding of the genes that contribute to PD, it will also be critical to understand the relationship between genetic contributions and influences of environmental toxicants. Possible areas of study could include further development of animal models of gene-environment interactions, the study of cohorts at high risk for PD (possible use of "hot spot" populations), prospective large-scale population studies involving collaborations between geneticists and epidemiologists, expanded evaluation of known cohorts (e.g., Nurses' Health Study, Physicians' Health Study, Honolulu-Asian Aging Study, Agricultural Health Study, 1999 Tanner et al. study of PD in twins, the Northern California Kaiser Permanente Medical Care Program, etc.), and/or a more comprehensive evaluation of familial and environmental clusters. Large-scale cohort studies may be prohibitively expensive at present, however other methods may be amenable to more immediate consideration.

Goal A: By the end of FY2003, establish an annual forum (e.g., workshop, conference) for the discussion/presentation of emerging topics in environmental influences in PD. (Low Risk/Short term) Primary Lead: NIEHS

Goal B: By the end of FY2003, issue a PAS on Gene-Environment interactions in PD and other Neurodegenerative Diseases. This PAS will encourage the development of novel animal models that combine genetic susceptibility with relevant exposures as well as the use of cutting edge technologies for identifying changes in genes, proteins and metabolites that link exposures to the death of specific neuronal populations. (Low Risk/Short term) Primary Lead: NIEHS

Goal C: By the end of FY2005, determine the feasibility of resampling cohort studies to include assessment of PD, and detailed exposure histories, within appropriate bioethical considerations (e.g., Nurses' Health Study, etc.). Encourage collaborations between existing funded PD epidemiologic cohorts to collect complementary genetic and risk exposure data (e.g., using administrative or competitive supplements). (High Risk/Short term) Primary leads: NIEHS, NINDS

Biomarker Development

Comments from participants at the July meeting: The development of biomarkers for PD has already been identified as a priority for the PD community. This issue could be addressed through several different approaches, including a more extensive investigation of possible peripheral markers for PD (e.g., in the blood), further evaluation of biomarkers through the field of proteomics, integration of biomarker investigations with ongoing clinical trials, and the development of a cohort at high risk for PD that could undergo a more in-depth assessment of biomarkers (e.g., imaging, cell loss, cerebrospinal fluid, etc.).

Goal: By the end of FY2005, evaluate the results of grants (funded publicly or privately) on biomarker development in order to determine if any of these approaches should be developed on a large scale. Incorporate models used successfully in the NINDS-sponsored neuroprotection clinical trial. (High risk/Short term) Primary leads: NINDS, The Michael J. Fox Foundation for Parkinson's Research